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<p>(54) Title: <b>DETERMINING CARDIAC OUTPUT</b></p> <p>(57) Abstract</p> <p>Cardiac output is determined by administering a respiratory gas for inhalation into a living body at a first location. Adsorption of optical radiation is then measured through living tissue at a location respiratorily downstream from the first location to determine an increase in circulated oxygen as a result of the increased oxygen. A system for determining cardiac output in a living body includes a source to administer a respiratory gas for inhalation into the living body at a first location and an oximeter connected to the living body at a location respiratorily downstream from the first location. The oximeter measures pulse rate and oxygen saturation of blood by means of adsorption of optical radiation through living tissue. A processor calculates circulation time (CT) or buildup time (T<sub>b</sub>) from the device measurements to determine cardiac output.</p>		

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## TITLE

## DETERMINING CARDIAC OUTPUT

## FIELD OF THE INVENTION

The invention relates to medical instrumentation. Particularly, the invention relates  
5 to a system and method for determining cardiac output.

## BACKGROUND OF THE INVENTION

Measurement of cardiac output is important in the evaluation, treatment and  
follow up of critically ill patients. Indicator-dilution methods are often used to measure  
cardiac output. Indicator-dilution techniques entail injection of an inert substance as  
10 an indicator into a circulatory system of the body and sampling of the indicator  
downstream from the injection site. The injection site is usually a systemic vein or the  
right side of the heart and the sampling site is often the pulmonary artery or a systemic  
artery, far enough downstream to allow adequate mixing.

Indicator-dilution techniques for measuring cardiac output are based on the  
15 assumption that after injection of a quantity of an indicator into the circulation, the  
indicator appears and disappears from any downstream location in a manner dependant  
on cardiac output. With high cardiac output, the indicator rapidly appears and washes  
out quickly at a downstream location. Indicator-dilution curves can be generated from  
serial or continuous measurement of the indicator concentration. Cardiac output then  
20 can be measured using the area under an indicator-dilution curves. Braunwald, *Heart  
Disease*, Chapter 6, pages 191-193, 5th Edition (1997). The Fick principle quantitizes  
this assumption by further assuming that the rate at which oxygen is consumed is a  
function of the rate of blood flow times the rate of oxygen pickup of red blood cells and  
that flow of blood in a given period of time is equal to the amount of substance entering

the stream of flow in the same period of time divided by the difference between concentrations of the substance in the blood upstream and downstream from its point of entry into the circulation.

Thermodilution is one of the most recent commonly utilized applications of the indicator-dilution method. Thermodilution requires an invasive procedure to obtain central venous access for insertion of a balloon floatation pulmonary artery catheter. The indicator, which is cold saline, is injected via the proximal port of the catheter into the right heart ventricle. A thermistor at the tip of the catheter positioned in the pulmonary artery, is the detector. A thermistor is a device to measure and record temperature. The thermistor detects temperature changes generated by injection of the cold saline indicator and produces indicator-dilution curves. Cardiac output is then determined from the curves.

Thermodilution procedures are invasive procedures requiring central venous access and injection via a catheter. Complications associated with such procedures include pneumothorax, air embolism and dysrhythmia, infections, thromboembolism and rupture of the pulmonary artery. Goldenheim *et al.*, *Cardiopulmonary Monitoring of Critically Ill Patients, The New England Journal of Medicine*, Sept. 20, 1984, pp.776-780. Several noninvasive techniques for estimating cardiac output have been developed, such as carbon dioxide rebreathing, electrical bioimpedance, Doppler ultrasonography and acetylene rebreathing. None is as reliable as the invasive standard procedure - thermodilution. Hence, there is a need for a noninvasive and reliable method for monitoring cardiac output. The present invention provides a noninvasive, risk free, economically feasible, time efficient and accurate means for monitoring cardiac output at the bedside or in an outpatient setting.

## SUMMARY OF THE INVENTION

The invention relates to a noninvasive method for monitoring cardiac output. In the method, a respiratory gas is administered for inhalation into a living body at a first location. Circulation time (CT) is determined as a measure of cardiac output at a second location. Circulation time (CT) is determined as a measure of cardiac output at a second location or buildup time ( $T_b$ ) is determined as a measure of cardiac output at the second location. CT is time between administration of the respiratory gas and detecting of an increase peak in concentration of the gas at the second location.  $T_b$  is time between first detecting of an increase in the respiratory gas at the second location to detecting an increase peak in concentration of the gas at the second location

10 In another aspect, the invention relates to a system for determining cardiac output in a living body. The system comprises a source to administer a respiratory gas for inhalation into the living body at a first location, a device to measure oxygen saturation of blood by means of adsorption of optical radiation through living tissue connected to the living body at a location respiratorily downstream from the first location and a processor  
15 that calculates circulation time (CT) or buildup time ( $T_b$ ) from the device measurements to determine cardiac output

The invention is more readily understood and appreciated by reference to the following Drawings.

## BRIEF DESCRIPTION OF THE DRAWINGS

20 FIG. 1 is an oxygen saturation (%) verses time (sec.) plot;

FIG. 2 is a plot comparing cardiac output as measured by an invasive methods to the inverse Lung to Finger Circulation Time (LFCT);

FIG. 3 is a plot comparing cardiac output as measured by an invasive methods to the to the inverse Buildup Time ( $T_b$ ) method;

FIG. 4 is a plot comparing cardiac output as measured by an invasive methods to the inverse Lung to Finger Circulation Time (LFCT);

FIG. 5 is a plot comparing cardiac output as measured by an invasive methods to the inverse Buildup Time ( $T_b$ ) method;

5        FIG. 6 is an oxygen saturation (%) verses time (sec.) plot (pulse administration of oxygen);

FIG. 7 is an oxygen saturation (%) verses time (sec.) plot (hypoxic gas administration followed by administration of oxygen); and

10        FIG. 8 is an oxygen saturation (%) verses time (sec.) plot (hypoxic gas administration followed by pulse administration of oxygen).

#### DETAILED DESCRIPTION OF THE INVENTION

Indicator-dilution techniques entail injection of an inert substance, the indicator, into the circulation and sampling of the indicator downstream from the injection site.

15        In the present invention, the lung and alveolar capillaries are used as an injection site and respiratory gas, preferably oxygen as an indicator. Change in oxygen saturation is monitored by an oximeter as a mode of detection of the indicator.

20        The transmission of light at a wavelength is a function of thickness, color and structure of skin, flesh, bone, blood and other material through which the light passes. This attenuation in transmission has a logarithmic characteristic in accordance with the Lambert-Beers Law. A pulse oximeter measures light transmission in pulsatile arterial blood and can be used to monitor arterial blood hemoglobin oxygen saturation. The pulse oximeter uses two different monochromatic light beams, which are emitted by light emitting diodes (ALEDs); one LED emitting light in the red wavelength range of about 645 nm, another LED emitting light in the infrared wavelength range of about

940 nm. Both beams are transmitted through an area of a patient's body. The pulse oximeter includes an oxygen saturation sensing probe which is arranged to be secured to a subject's finger or ear. Usually, the probe has the form of a clip including both LEDs and a light detector. The probe is arranged so that the single light detector  
5 receives the light of both LEDs after the light has passed through the patient's body. The light of both LEDs is attenuated by static and dynamic absorbers on its path through the patient's body to the light detector. The quantity of arterial blood varies with time synchronously with a patient's heartbeat and represents the only dynamic absorber during the pulse period. All other absorbers, such as skin, tissue or bone, are  
10 not time-variant.

The light detector, which may be a photodiode, receives attenuated light of each wavelength. Signals produced by the diode in response to the light, are amplified, low pass filtered, converted from analog to digital and further processed by a microprocessor. A pulse finding algorithm analyses the received signals, which are  
15 called spectrophotometric signals to identify and determine pulse. After identifying pulse, the microprocessor determines diastolic and systolic values of the spectrophotometric signals and derives relative absorption ratios. The microprocessor computes arterial oxygen saturation from the relative absorption ratio using calibration data and extinction coefficients from the absorption spectrum of hemoglobin and  
20 oxyhemoglobin at the appropriate wavelengths.

Goodenday *et al.*, Noninvasive Measurement of Cardiac Function during Exercise, Using Resaturation Curves, *Chest* 1976, 70, 6, pages 732-739, discloses a noninvasive indicator-dilution test, namely resaturation curves to detect rate of change in arterial oxygen saturation in an exercising subject during breathing of various

concentrations of oxygen. A mild hypoxia is induced in the subject followed by administration of 100% oxygen to abruptly cause resaturation of blood hemoglobin.

Changes in arterial oxygen saturation ( $\text{SaO}_2$ ) are recorded with an oximeter.

Goodenday *et al* determines a time constant,  $\tau$  as the time required for  $\text{SaO}_2$  to rise 63  
5 percent of the distance to its final equilibrium value. Goodenday *et al* also defines a  
clearance function  $\text{SV}/\text{V}$  that is inversely proportionate to the quotient  $(\tau)(\text{HR})$  where  
HR is heart rate. Goodenday *et al* reports a study that compared normal subjects with  
patients with cardiac valve disease and concluded that  $\tau$  decreases with increasing  
cardiac output while the clearance function ( $\text{SV}/\text{V}$ ) decreases with impairment of  
10 cardiac function during exercise.

According to the present invention, cardiac output is determined with a system  
that includes a reparatory gas source to provide an increased gas concentration for  
inhalation into a living body at a first location and a device to measure optical radiation  
through a living body at a location respiratorily downstream from the first location.

15 Preferably, the respiratory gas is oxygen and the device to measure optical radiation  
is an oximeter. A change in inspired oxygen concentration leads to detection of a  
change in oxygen saturation measured by the pulse oximeter after a period of time  
delay. This time delay between administration of the oxygen indicator into the lungs  
and its detection in the systemic capillaries, namely the circulation time, is then  
20 measured. This measurement (CT) has been found to correlate to cardiac output as  
measured by the thermodilution method. Buildup Time ( $T_b$ ) is the time from  
appearance of an indicator to its peak concentration. According to the present  
invention, this factor has also been found to correlate to cardiac output as measured by  
the thermodilution method.



CT and  $T_b$  can be determined by any one of several methods that are embraced within the present invention. A first method includes continuous monitoring of oxygen saturation ( $SaO_2$ ) in a subject for approximately 1-2 minutes while the subject is lying still in a supine or sitting position to establish a baseline oxygen saturation level. Then  
5 a higher concentration of oxygen or 100% supplemental oxygen is administered via an oxygen mask, a partial rebreathable mask or a non-rebreather mask. The gas can also be administered by any type of face mask, nasal cannula, through an endotracheal tube, by means of an oxygen tent or the like. Thus for example, if a patient is on a ventilator, 100% oxygen can be administered through the endotracheal tube via the  
10 ventilator.

The subject's oxygen saturation ( $ASaO_2$ ) is recorded by an on-line computer and CT and  $T_b$  are measured and determined by a computer. In another embodiment, the subject is administered a pulse of supplemental oxygen in the form of a known number of breaths of 100% oxygen or a known volume of 100% oxygen followed by  
15 a return to room air breathing.

Subjects with low baseline oxygen saturation exhibit a high signal to noise ratio and an increase in dynamic range in the first portion of the oxygen saturation versus time curve thus making measurement of CT and  $T_b$  easier and more accurate. In another method, the signal is augmented by administering a few breaths of hypoxic gas  
20 to decrease the subject's baseline  $SaO_2$  followed by the administration of continuous 100% supplemental oxygen via a non-rebreather mask. An hypoxic gas is a gas with decreased oxygen level. Hypoxic gas mixtures are typically made using a combination of oxygen and nitrogen. Room air contains approximately 21% oxygen with nitrogen as the majority of the remaining gas. A mixture that contains less than 21% oxygen

is a hypoxic gas mixture. Typically, a gas mixture containing 10% oxygen is used in experiments involving human subjects. In one embodiment of the present invention, a subject receives a pulse of 100% supplemental oxygen following the hypoxic gas administration.

5           The invention is illustrated by the following examples.

#### **EXAMPLES**

Studies were conducted to measure cardiac output of various subjects to compare the methods of the invention with the thermodilution method.

10           Fourteen male and eight female subjects who were undergoing diagnostic right heart catheterization for clinical indications participated in the studies. The subjects= ages ranged between 21-81 years with a mean of  $51.9 \pm 14.3$ , their weights ranged between 61-123 kg with a mean of  $90.1 \pm 20.5$  and their heights ranged between 152-185 cm with a mean of  $169.8 \pm 9.2$ . The subjects= medical profiles included dilated  
15   angina, coronary artery disease, atrial fibrillation, renal failure, diabetes mellitus and congestive heart failure. Two of the subjects already had an indwelling Swan Ganz catheter and 20 were studied immediately before or after right heart catheterization

Cardiac output was measured 3-5 times by the thermodilution method. A pulmonary artery balloon flotation catheter (Baxter Corporation) was placed in either  
20   the right or left pulmonary artery under fluoroscopic guidance. Thermodilution was performed with the use of a cardiac output computer (Baxter Corporation) connected to a thermister at the tip of the pulmonary artery catheter. For each measurement, 10 cc of room temperature normal saline was injected into the proximal port of the

pulmonary artery catheter. The result reported by a cardiac output computer was recorded.

Three measurements within 10% of the mean or average of five measurements was used as an acceptable value for cardiac output. Nine patients had moderate to  
5 severe tricuspid regurgitation. Since cardiac output measurements by thermodilution method may not be accurate in the presence of tricuspid regurgitation, the Fick method of estimating cardiac output utilizing measured pulmonary artery saturation and direct arterial saturation was used for these subjects. The Fick method of determining cardiac output was performed using standard methods of measuring oxygen content of arterial  
10 mixed venous blood and oxygen consumption either measured directly or estimated based on the patient's demographics. Cardiac output was calculated as oxygen consumption divided by arterial-venous oxygen content difference.

Cardiac output was then monitored by the system of the invention. A finger probe connected to an Ohmeda 3740 pulse oximeter was placed on either the index or  
15 the middle finger of the subject lying supine in bed. Oxygen saturation was recorded continuously via an on-line computer at 25 Hz per channel. A second channel was used as a marking channel. The marking channel is a recording with two levels - on and off. The marking channel was on when oxygen was administered and off when discontinued to provide a high voltage mark at onset of administration of 100% oxygen  
20 thereby generating a vertical line on the oxygen saturation plot to serve as a designation of time of onset of oxygen administration. The subject's baseline oxygen saturation was recorded for approximately one minute. Three deep breaths of 100% oxygen via a nonrebreather oxygen mask were then administered and the subject's oxygen saturation was recorded for another 3-4 minutes. The initiation of the first breath of

oxygen was labeled via the marking channel on an oxygen saturation plot. This protocol was repeated 3-5 times and a mean of the values was calculated. Following administration of 100% oxygen, the subject's oxygen saturation was monitored by finger pulse oximetry. The oxygen saturation was observed to rise, peak and return to baseline, as in other indicator dilution methods. See FIG. 1.

Two different components of oxygen saturation curves were blindly analyzed. First, the time interval between initiation of the first breath of 100% oxygen and the peak in the oxygen saturation plot (CT) was measured. In these Examples, LFCT is CT for ALung to Finger Circulation Time. Second, the time from onset of a rise from baseline in the oxygen saturation curve to peak oxygen saturation was measured. This component is  $T_b$ .  $T_b$  is illustrated in FIG. 1, which is an oxygen saturation (%) versus time (sec.) plot as recorded by an on-line computer. The shaded area depicts time interval for administration of three breaths of 100% oxygen. The LFCT of oxygen was measured from the onset of 100% oxygen administration to peak in oxygen saturation.  $T_b$  was measured from the onset of rise in oxygen saturation to the peak in oxygen saturation.

Cardiac output values obtained by the thermodilution method were compared with the inverse of LFCT and  $T_b$  values by linear regression analysis for paired data. Regression analysis was done using software package SPSS 7.5.1 for Windows™. The statistical analysis included calculation of R or coefficient of R probability values and standard estimate of error. All values for measured parameters in the studies were expressed as mean  $\pm$  standard deviation.

In the drawings, FIG. 2 is a comparison of cardiac output as measured by thermodilution to inverse LFCT in 22 subjects. FIG. 3 is a comparison of cardiac output as measured by thermodilution to inverse  $T_b$  in 22 subjects.

FIG. 4 is a comparison of cardiac output as measured by thermodilution to  
5 inverse LFCT in 13 subjects with baseline oxygen saturation less than or equal to the median baseline oxygen saturation (95%). FIG. 5 is a comparison of cardiac output as measured by invasive methods to inverse LFCT in 9 subjects with baseline oxygen saturation greater than the median baseline oxygen saturation (95%).

In the study illustrated in FIG. 6, the subject received a pulse of 100%  
10 supplemental oxygen in the form of a known number of breaths of oxygen via a non-rebreather mask or a known volume of oxygen followed by room air breathing. In the study illustrated in FIG. 7, a few breaths of hypoxic gas were first administered to decrease the subject's baseline  $SaO_2$  followed by continuous 100% supplemental oxygen administration via a non-rebreather mask. In the study illustrated in FIG. 8,  
15 hypoxic gas was first administered followed by a pulse of 100% supplemental oxygen via a non-rebreather mask.

The results of the studies were reported as range, mean  $\pm$  standard deviation.

The measured parameters were reported along with R, correlation coefficient, and P-value, probability value. The median was the value at which half the measurements  
20 were greater than and half the values were less than the reported value. R is the correlation coefficient, a statistical value to describe how well the data are represented by an equation of a straight line. A group of values that form a perfect line have an R value of 1. A group of values that are randomly distributed have an R value of 0. The p value is a statistical representation of the probability that there is some relationship

between two variables, such as LFCT and cardiac output. The p value represents the probability of what is referred to as the null hypothesis, or that two variables under study are not related to one another. In the present studies, p was less than 0.001. In other words, there is greater than a 99.9% chance that the null hypothesis is not applicable and the two variables are related to one another.

The comparison of LFCT and  $T_b$  with cardiac output measured by the thermodilution method resulted in an LFCT range of 35.2-136.4 seconds, with mean LFCT at  $52.8 \pm 20.8$  seconds and  $T_b$  range of 12.6-56.7 seconds with mean  $T_b$  of  $21.0 \pm 9.1$  seconds. The subjects' cardiac output as measured by thermodilution ranged from 2.6 to 8.0 L/min with mean cardiac output of  $5.1 \pm 1.3$  L/min. The LFCT (sec) inversely correlated in a linear fashion with thermodilution measured cardiac output ( $R=0.76$ ,  $p < .001$ ) (FIG. 3). Furthermore, the inverse of  $T_b$  ( $\text{sec}^{-1}$ ) also correlated in a linear fashion with the cardiac output ( $R=0.72$ ,  $p < .001$ ) (FIG. 3).

Mean baseline oxygen saturation was  $94.5 \pm 2.2$  with the median at 95%. Secondary to low signal to noise ratio in subjects with high baseline oxygen saturation, the subset of subjects with baseline oxygen saturation at or below the median (13 of 22 subjects), was analyzed separately and compared to those with baseline oxygen saturation greater than the median (9 of 22 subjects). Stronger correlation was observed among the measurements of LFCT with cardiac output in subjects with lower baseline oxygen saturation ( $R=0.87$ ,  $p < 0.001$ ) (FIGs 4 and 5).

These studies demonstrate that measurement of oxygen Lung to Finger Circulation Time (LFCT) as well as its Buildup Time ( $T_b$ ) are inversely proportional to cardiac output as measured by a standard invasive technique. Measuring cardiac output according to either Lung to Finger Circulation Time (LFCT) or Buildup Time

(T<sub>o</sub>) is safe due to the use of oxygen as the indicator and its noninvasive nature. Furthermore, these determinations are inexpensive and practical since they utilizes detection by oximeters, which are commonly found in the hospital and clinical settings.

Other modifications of the present invention will occur to those skilled in the art  
5 subsequent to a review of the present application. These modifications and equivalents thereof are intended to be included within the scope of this invention.

## CLAIMS

What is claimed:

1. A method of determining cardiac output, comprising:
  - (A) administering a respiratory gas for inhalation into a living body at a first  
5 location; and
  - (B) determining circulation time (CT) at a second location as a measure of cardiac  
output.
2. The method of claim 1, wherein CT is time between administration of said  
respiratory gas and detecting of an increase peak in concentration of said gas at said  
10 second location.
3. The method of claim 1, comprising measuring oxygen saturation to  
establish a baseline oxygen saturation level.
4. The method of claim 1, wherein (A) comprises continuously administering  
an increased oxygen.
- 15 5. The method of claim 1, wherein (A) comprises administering an increased  
oxygen in pulses.
6. The method of claim 1, wherein (A) comprises administering a hypoxic gas  
to decrease a baseline saturated oxygen level and then continuously administering an  
increased oxygen.
- 20 7. The method of claim 1, wherein (A) comprises administering a hypoxic gas  
to decrease a baseline saturated oxygen level and then administering an increased oxygen  
in pulses.
8. The method of claim 1, further comprising calculating cardiac output as a  
function of CT.



9. The method of claim 1, comprising monitoring cardiac output according to said CT.
10. The method of claim 10, comprising determining oxygen saturation of blood from said adsorption of optical radiation.
- 5 11. The method of claim 2, further comprising detecting said increase peak in said gas by measuring adsorption of optical radiation per time through living tissue at a location respiratorily downstream from said first location to determine change in circulated oxygen concentration per time as a result of administration of said respiratory gas.
12. The method of claim 11, wherein said adsorption of optical radiation is  
10 measured by an oximeter that emits optical radiation into said tissue and detects optical radiation at an exit from said tissue.
13. The method of claim 12, comprising generating a spectrophotometric signal by means of said oximeter and deriving arterial hemoglobin oxygen saturation from said spectrophotometric signal
- 15 14. A method of determining cardiac output, comprising:  
(A) administering a respiratory gas for inhalation into a living body at a first location; and  
(B) determining buildup time ( $T_b$ ) at a second location as a measure of cardiac output.
- 20 15. The method of claim 14, wherein  $T_b$  is time between first detecting of an increase in said respiratory gas at said second location to detecting an increase peak in concentration of said gas at said second location.
16. The method of claim 14, further comprising calculating cardiac output as a function of  $T_b$ .

17. The method of claim 14, comprising measuring oxygen saturation to establish a baseline oxygen saturation level.

18. The method of claim 14, wherein (A) comprises continuously administering an increased oxygen.

5 19. The method of claim 14, wherein (A) comprises administering an increased oxygen in pulses.

20. The method of claim 14, wherein (A) comprises administering a hypoxic gas to decrease a baseline saturated oxygen level and then continuously administering an increased oxygen.

10 21. The method of claim 14, wherein (A) comprises administering a hypoxic gas to decrease a baseline saturated oxygen level and then administering an increased oxygen in pulses.

22. The method of claim 14, further comprising first detecting said gas and detecting said increase peak of said gas by measuring adsorption of optical radiation per  
15 time through living tissue at a location respiratorily downstream from said first location to determine change in circulated oxygen concentration per time as a result of administration of said respiratory gas.

23. The method of claim 22, comprising determining oxygen saturation of blood from said adsorption of optical radiation.

20 24. The method of claim 22, wherein said adsorption of optical radiation is measured by an oximeter that emits optical radiation into said tissue and detects optical radiation at an exit from said tissue..

25. The method of claim 24, comprising generating a spectrophotometric signal by means of said oximeter and deriving arterial hemoglobin oxygen saturation from said spectrophotometric signal

26. A system for determining cardiac output in a living body, comprising;

5 (A) a source to administer a respiratory gas for inhalation into a living body at a first location;

(B) a device connected to said living body at a location respiratorily downstream from said first location for measuring oxygen saturation of blood by means of adsorption of optical radiation through living tissue; and

10 (C) a processor that calculates circulation time (CT) or buildup time ( $T_b$ ) from said device measurements to determine cardiac output.

27. The system of claim 26, wherein said device comprises a spectrophotometric signal generator and said processor comprises a computer for deriving arterial hemoglobin oxygen saturation from a spectrophotometric signal.

15 28. The system of claim 26, wherein said device comprises a finger or ear pulse probe connected to a pulse oximeter.

29. The system of claim 26, additionally comprising a graphics means to plot and display continuous oxygen saturation measurements against time.

20 30. The system of claim 26, additionally comprising an hypoxic gas source and a switch to change from said oxygen source to said hypoxic gas source.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US99/08539

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC(6) :A61B 5/00 US CL :600/323 According to International Patent Classification (IPC) or to both national classification and IPC														
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) U.S. : 600/309, 310, 322, 323  Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)														
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>														
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.												
Y	US 5,299,579 A (GEDEON et al) 05 April 1994, col. 6 line 57 to col. 7 line 2.	1-5, 8-19, 22-29												
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.														
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Date of the actual completion of the international search 09 JUNE 1999		Date of mailing of the international search report 28 JUN 1999												
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